Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose

Office of Pesticide Programs

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This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs) and conducting cumulative risk assessments (CRA).

1.0. Background

Section 408(b)(2)(D)(v) of the Federal Food, Drug, and Cosmetic Act (FFDCA) requires EPA to take into account "available evidence concerning the *cumulative effects* of such [pesticide] residues and other substances that have a *common mechanism of toxicity".* The Office of Pesticide Programs (OPP) has developed two guidance documents:

- *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) which describes the process for establishing CMGs;
- *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002) which describes the steps used in conducting CRA.

The process described in these documents results in a highly refined CRA but requires an extensive amount of resources, large amounts of toxicology and exposure data, and may involve sophisticated modelling. The process involves developing science policy documents that establish a CMG before conducting a highly refined CRA. To date, OPP has established five CMGs: organophosphates (OPs), *N*-methyl carbamates (NMCs), chloracetanilides, triazines, and naturally occurring pyrethrins and synthetic pyrethroids[1]. CRAs have been conducted on each group (http://www.epa.gov/oppsrrd1/cumulative/).

The level of refinement provided by this approach is not necessary or even feasible for all existing pesticide classes. The 2002 CRA guidance notes that not all cumulative assessments need to be of the same depth and scope and that it is important to determine the need for a comprehensive risk assessment by considering the exposure profile. The 2011 WHO IPCS[2] guidance on CRA describes a screening approach involving tiered analysis with increasing levels of refinement. (Meek et al, 2011). The Agency is developing this guidance to assist scientists and decision-makers in screening pesticides for potential common mechanism groupings and conducting screening-level CRAs, neither of which is provided for in either guidance document listed above. Specifically, this document provides guidance for screening available information to identify groups of pesticides that may have a common mechanism of toxicity (i.e., candidate CMGs). In addition, this document provides guidance for screening available information on

[1] The agency has evaluated the thiocarbamates & dithiocarbamates and found that these pesticides did not share a common mechanism. http://epa.gov/pesticides/cumulative/thiocarb.pdf; http://epa.gov/oppsrrd1/cumulative/dithiocarb.pdf

[2] IPCS: International Programme on Chemical Safety, http://www.who.int/ipcs/en/

those candidate groups for potential cumulative risks, which may lead to more refined CRAs. This document relies on the policies and principles provided in the CMG and CRA guidance documents along with expertise and knowledge gained by OPP in the conduct of the five CRAs noted above.

2.0. Key Terms in Establishing a Common Mechanism Grouping & in CRA

A CRA begins with the identification of a group of pesticide chemicals, referred to as a CMG, that induce a common toxic effect by a common mechanism of toxicity. OPP has guidance documents for designating CMGs (USEPA 1999) and for developing CRAs (USEPA 2002). These documents provide definitions for some key concepts:

- OPP's CMG guidance defines **mechanism of toxicity** as the major steps leading to a toxic effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required in order to describe a mechanism of toxicity. For example, a mechanism of toxicity may be described by knowing the following: a chemical binds to a given biological target *in vitro,* and causes the receptor-related molecular response; *in vivo* it also leads to the molecular response and causes a number of intervening biological and morphological steps that result in an adverse effect.

  This definition of mechanism of toxicity is similar to the concept of mode of action (MOA) as defined by EPA's Cancer Guidelines (USEPA, 2005) and other international efforts thru OECD and WHO (Boobis et al., 2008; Seed et al., 2005; Sonich-Mullin et al., 2001; Meek et al, 2014). In addition, the term, adverse outcome pathway (AOP), has been introduced (Ankley et al., 2010). An AOP links a molecular initiating event (MIE) to progressive levels of biological organization at the individual or population level. As such, although the terminology is different, the concepts are similar---an AOP is conceptually similar to establishing key events in a MOA or for establishing a CMG under the FFDCA. In this document, both terms (MOA and AOP) are used.

- **A common mechanism of toxicity** as defined in EPA's CMG and CRA guidance pertains to two or more pesticide chemicals or other substances that cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each pesticide chemical. A CMG is a group of pesticides which share a common mechanism of toxicity**.**

- **A common mechanism endpoint(s)** is/are those common toxic effect(s) which are pertinent and sensitive endpoints associated with the common mechanism which will provide a scientifically sound basis for determining relative potency of chemicals in a CRA.

- **Candidate common mechanism group** or candidate CMG represents a group of pesticides for which toxicological information on chemical structure, apical endpoint, pesticidal MOA and/or mammalian mechanistic information suggest the potential for a common mechanism of toxicity but do not have adequate data for establishing key events in a pathway as described in the MOA/AOP framework (e.g., lack of dose or temporal concordance of proposed key events).

3.0. Cumulative Risk Screening Analysis

A screening-level assessment applies more conservative approaches and health protective overestimates of toxicity and/or exposure than would a refined CRA conducted using the 2002 CRA guidance. The screening analysis for CRA described in this guidance begins with an evaluation of the toxicological knowledgebase available on a particular group of pesticides derived from experimental toxicology studies submitted for pesticide registration and from the scientific literature. If the toxicological characterization of potential for common mechanism suggests a candidate CMG may be established, then a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure. Together, the initial toxicological and exposure analyses lead to different options for next steps described below.

3.1. Toxicological determination of whether a CMG or Candidate CMG can be Established

3.1.1. Toxicological Considerations in Determining a Candidate CMG

The 1999 CMG guidance indicates that evaluating a group of pesticides for potential common mechanism of toxicity begins with several considerations: chemical structural similarity, toxicological profile, and information on MOA/AOP. The screening approach uses the same considerations. The degree of available information will vary across pesticides. For some, there is extensive knowledge of MOA/AOP while for others, little to no information is known on how they interact with biological targets in any taxa. In other words, little to no information is known on the pesticidal MOA or mammalian MOA/AOP. For such pesticides, the available data needs to be carefully considered before conducting a cumulative screening evaluation.

3.1.1.1. Chemical Structural Similarity

Shared chemical structure may be a good starting point for considering a group of chemicals. In many cases, shared chemical structure may translate to shared toxicophore[3] and ultimately to a common mechanism of toxicity. However, shared chemical structure does not guarantee a shared toxicological profile. Chemical structure needs to be evaluated in combination with other considerations. *Shared chemical structure is not solely sufficient as support for considering a candidate CMG.*

[3] A toxicophore is a feature or group within a chemical structure that is associated with toxic properties

3.1.1.2. Hazard Profile

As part of CRA screening efforts, reviewers conduct an initial review of the experimental toxicology data from data submitted for pesticide registration and from the scientific literature for a particular group of pesticides. The reviewer evaluates data on all available durations of effects, routes of exposure, species tested, and potentially sensitive lifestages. The target organ(s), adverse effects/apical outcome(s), and pharmacokinetic properties are identified and compared among the group members. Specifically, the reviewer is evaluating the extent to which common patterns of effects are observed among members of a potential class. Those effects at lower doses, particularly those used in deriving points of departure (PoDs) for single pesticide risk assessment, get more weight in the screening analysis than high dose effects. Toxic effects related to specific target sites (e.g., particular enzyme or other protein, hormone) or target tissues (e.g., thyroid, blood) are preferred over non-specific effects (e.g., changes in body weight or food consumption) since specific effects are more likely to be derived from common toxicity pathway than non-specific ones. Non-specific toxic effects, unless tied to a MOA/AOP or testable hypothesis related to a potential MOA/AOP, would not support a candidate CMG.

In most cases, common apical outcome will not be used as the sole factor in determining a candidate CMG for screening purposes. For example, all neurotoxic pesticides will not be grouped into a single group for screening purposes. Neurotoxicity is mediated through multiple pathways and under the FFDCA only those which share a common pathway are combined. Therefore, it is inappropriate to include all neurotoxic pesticides in a single candidate group for cumulative screening. Similarly, all pesticides which cause liver or kidney toxicity will not be combined in a candidate CMGs since liver and kidney toxicity is often the result of repeated exposure to high doses which overwhelm the biological system; moreover, kidney and liver effects can occur from multiple pathways. Common adverse effects to the liver and kidney will be evaluated carefully in the context of knowledge of mammalian MOA/AOP and chemical structure.

3.1.1.3. MOA/AOP/Common Mechanism of Toxicity

Across different pesticide classes, a range of mechanistic information is available.

Data & knowledge of *mammalian MOA/AOP* and related information on pharmacokinetics for individual members of the pesticide class provides the strongest information and is the foundation for establishing a CMG. The CMG guidance describes this process in detail; only key information is summarized here.

Use of the modified Bradford Hill Criteria like those described in the MOA framework (USEPA, 2005; Boobis et al., 2008; Seed et al., 2005; Sonich-Mullin et al., 2001) provides the organizational tool for evaluating the availability of data and describing the key events and dose response and temporal concordance linkage of those key events leading from exposure to adverse health outcomes. Specifically, the modified Bradford Hill Criteria are used to evaluate

the experimental support that establishes key events within a MOA or an AOP, and explicitly considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight of evidence (WoE) analysis. The ability to establish the MOA/AOP across representative chemicals within the group is a key determinant for establishing a CMG.

With respect to screening for candidate CMGs, existing knowledge of an established MOA/AOPs for one or more individual members of the group is a strong starting point. The mechanistic information and apical outcomes for the remaining candidate CMG member(s) can then be used to compare with similar information on those with the more robust data. For those classes where no members have an established MOA/AOPs but some limited mechanistic information is available, a determination is made about the extent to which a testable hypothesis can be described.

For pesticide classes which lack data on the mammalian MOA/AOP, information on the pesticidal MOA may provide a useful a starting point in for purposes of screening. Consideration of the pesticidal MOA needs to be done with caution as some pesticidal MOAs may not be relevant to humans or have unknown relevance. For example, the sulfonyl urea (SUs) herbicides share the ability to inhibit acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids (valine, leucine, and isoleucine), all of which are essential for plant growth. Mammals have ALS but its function in mammals is unknown. In toxicity studies with SUs, effects are generally observed at very high doses (at or near the limit dose for many SUs). In addition the SUs do not show a common toxicological profile; instead target organs vary among this class. Thus, the toxicological profile of the SUs does not support a candidate CMG determination.

3.1.2. Drawing Conclusions from CMG Screening Analysis and Options for Further CRA

OPP will conduct a WoE analysis to evaluate all relevant scientific information, as described in 3.1.1, along with the strengths and limitations of the evidence. Use of the MOA/AOP framework provides the organizing principles (e.g., dose concordance, temporal concordance, specificity, biological plausibility, etc) for assessing the degree to which the available evidence does or does not support common toxicological profile(s) and the degree to which data support establishing a set of key events. As shown in Figure 1, this analysis can lead to various options for next steps (Figure 1).

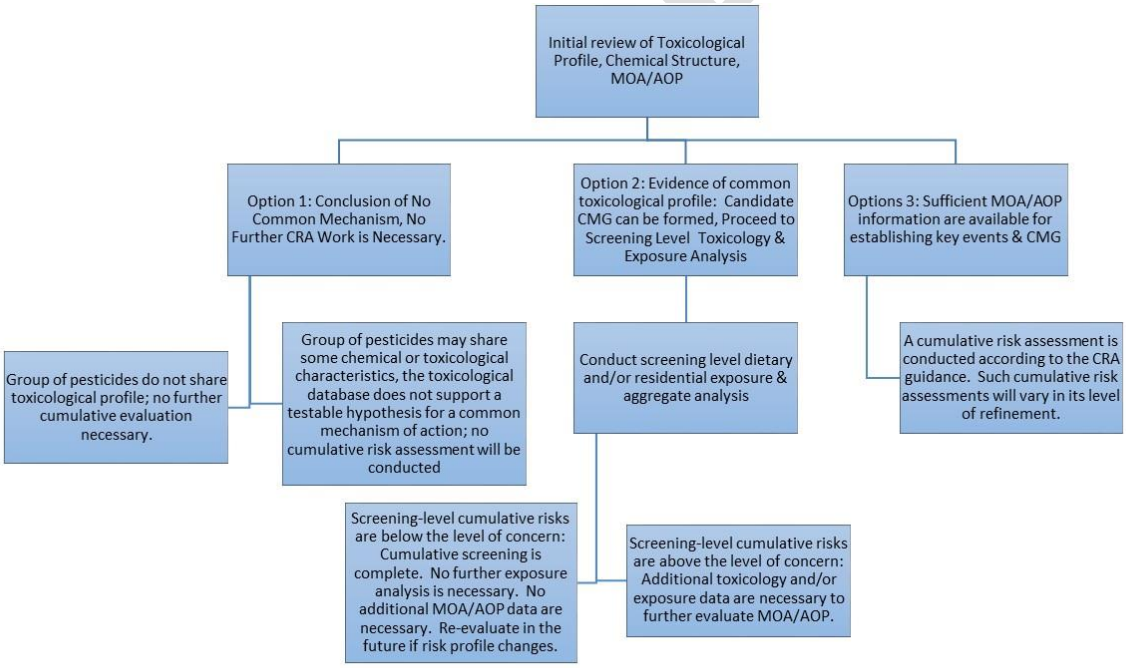
Option 1: Conclusion of No Common Mechanism, No Further CRA Work is Necessary:

- For some pesticide groups, the pesticides do not share a similar toxicological profile and no further cumulative evaluation is necessary.
- For other groups, although the pesticide members may share some chemical or toxicological characteristics (e.g., chemical structure or apical endpoint), the toxicological database does not support a testable hypothesis for a common mechanism of action. In these cases, the Agency will conclude that no common mechanism of toxicity exists for this group of pesticides and that no CRA will be conducted.

Option 2: Candidate CMG can be formed; Screening-Level Exposure Analysis is Conducted: Candidate CMGs are groups of pesticides that have shared characteristics to support a testable hypothesis for a common mechanism of action or sufficient toxicological data to suggest a common pathway but do not have adequate data for establishing key events in a pathway as described in the MOA/AOP framework (e.g., lack of dose or temporal concordance of proposed key events). For these, a screening-level exposure analysis will be conducted as described in section 3.2 below.

Option 3: CMG can be established: Sufficient mechanistic data are available to support establishing a set of key events in a pathway and thus support developing a science policy establishing a CMG; such policy may be developed according to the 1999 CMG guidance document. Following the development of that science policy, a CRA will be conducted. This CRA would follow the CRA guidance and thus no additional information is provided in this document.

Figure 1. Draft, Schematic for the Cumulative Risk Assessment Screening Framework



3.2. CRA Screening on a Candidate CMG

If a candidate CMG can be formed (Option 2), the Agency will generally proceed to a CRA screening-level analysis as described below.

3.2.1. Toxicology Evaluation in CRA Screening

Consistent with the Agency's mixture risk assessment guidance (USEPA 1986; USEPA, 2000), OPP assumes dose additivity in CRA unless data are available to support an alternative approach. Then OPP will evaluate the toxicological database for dose response data to identify an index chemical and to develop screening-level relative potency factors (RPFs) and PODs for purposes of screening exposure analysis. The data and mathematical approach used in the derivation of the screening RPFs and PODs should be described and include a characterization of their refinement (or lack thereof). Screening-level RPFs and PODs should, to the extent possible, be related to hypothesized MOA/AOP and the common toxic effect for the class.

While under the 2002 CRA guidance, an important component in cumulative hazard assessment is the derivation of a uniform measure of dose response such that the potency of each CMG member is accurately assessed, in this screening-level cumulative analyses, RPFs and PODs may vary in their level of refinement. For example, these toxicity values may be derived from the PODs from single chemical risk assessments, from no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) from specific toxicology studies or possibly benchmark doses (BMDs). In some analyses, the same value may be used for each chemical in the candidate group.

3.2.2. Exposure Considerations in CRA Screening

The screening process continues by evaluating the exposure and risk potential using the most recent single chemical risk assessments. Evaluation of these risk assessments includes consideration of the registered use patterns, level of refinement, and overall risk profiles of the candidate CMG being considered.

3.2.2.1. Use Pattern

Defining and comparing the use patterns of the chemicals within a candidate CMG is an important task. The range of food and residential uses for the chemicals within the candidate CMG is characterized. One key consideration is the extent to which food uses for the candidate CMG pesticide chemicals are similar (e.g., all the pesticide chemicals have a registered apple or corn use) or wide-ranging. Another important consideration is if the candidate CMG chemicals have residential uses. Given that pesticide chemicals within a same class are likely to control similar pests, evaluation of the use patterns and use sites may allow for the co-occurrence of candidate CMG pesticide chemicals to be considered.

3.2.2.2. Level of Refinement for Single Pesticide Chemical Risk Assessment

Determining the level of refinement used in each single pesticide chemical risk assessment is a key task when working through the screening analysis. For example, in evaluating the single pesticide chemical food exposure assessments, it is important to characterize the type of data used to define food residues [i.e., tolerance levels, field trial data, or the Pesticide Data Program (PDP) data] and whether or not percent crop treated information was incorporated. Additionally, determination of the use of chemical-specific exposure or residue data in the single chemical residential assessments should be considered. When combining individual chemical-specific exposure assessments, comparison of the levels of refinement across the pesticide chemicals within the candidate CMG should be considered in the interpretation of the screening evaluation.

3.2.2.3. Single Pesticide Chemical Aggregate Assessment Risk Profile

Determining the risk profile for each single pesticide chemical risk assessment is also a key task in the screening analysis. It is important to consider the relative contributions of each exposure pathway (e.g., food, drinking water, and residential exposure) as well as the overall aggregate risk picture for each pesticide chemical. This analysis can suggest areas of refinement which might have the greatest impact on the screening evaluation.

3.2.3. Tiered Approach for Cumulative Screening-Level Dietary Exposure Analysis

This section presents a variety of approaches that could be considered for screening-level analysis of cumulative risks of a candidate CMG. These approaches are presented in a tiered manner attempting to account for the resources that are required to conduct the analysis. If a minimal resource approach can be used and cumulative screening risks are acceptable, there is no need to perform more refined approaches. As such, the reviewer follows through the tiers described below until the screening risk does not exceed the level of concern.
The starting point for the screening-level cumulative analysis is to use the exposure values derived from the single pesticide chemical assessments, regardless of level of refinement or difference in levels of refinement across the pesticide chemical candidate CMGs; therefore, considering the levels of refinement will be a key component in interpreting the screening results. Most food exposure assessments that are conducted by OPP for conventional pesticides are unrefined, relying on tolerance level residues and assuming 100% of the crop is treated. However, in cases where risks have been identified and refinements are needed, OPP's general policy is to refine only to the degree that risks of concern have been mitigated. Consequently, often, single pesticide chemical dietary assessment are unrefined or only partially refined. Any refinements discussed in the dietary tiers below would be in addition to those already in place in the single pesticide chemical assessments. Conceptually, the reviewer will systematically work through the tiers described below and stop refinements at the point when the dietary risk does not exceed the level of concern.

- *Tier 1:* Combined food and water exposures from the most recent single pesticide chemical risk assessment(s) are extracted and summed. The summed residue value is then compared to the POD of the most potent member of the candidate CMG. This approach is the least resource intensive but the most likely to grossly overestimate the cumulative risk picture. Tier 1 assumes complete co-occurrence of both food and drinking water residues and that all members of the candidate CMG are equivalent toxicologically to the most potent member.
- *Tier 2:* Combined food and water exposures from the most recent single pesticide chemical risk assessment(s) are extracted, RPF scaled, and summed. This residue value is then compared to the POD of the reference chemical. While this method considers the relative toxicity of each member of the candidate CMG pesticide chemicals, this approach is still likely to significantly overestimate the cumulative risk picture. Tier 2 assumes complete co-occurrence of both food and drinking water residues.
- *Tier 3:* In Tier 3, food residues are handled the same as in Tiers 1 and 2, above. However, Tier 3 addresses the unlikely co-occurrence of high-end residues in drinking water. To accomplish this, drinking water residues are removed from all single pesticide chemical dietary exposure assessments. The single highest RPF-scaled modeled water exposure scenario from among the members of the candidate CMG is identified and is combined with the RPF-adjusted combined food exposures. While requiring additional resource expenditure, this approach incorporates relative toxicities and more appropriately addresses drinking water exposure, while still overestimating exposure by assuming complete co-occurrence of food residues.
- *Tier 4:* In tier 4, water residues are handled as in tier 3. However, an attempt is made to refine co-occurrence of food residues. Only the pesticide that has the highest RPF-scaled exposure would be used for a given crop/commodity. For example if multiple pesticides are used on apples, only the chemical that yields the highest RPF-scaled exposure would be included in the cumulative screening evaluation. The assumption is that growers would not use multiple pesticide chemicals from the same pesticide chemical class in the same season. While requiring further resource expenditure, this approach incorporates relative toxicities and begins to address the unlikely co-occurrence of candidate CMG pesticide residues in food and/or water. However, this screening-level assessment likely still uses modelled drinking water residue estimates and may not actually include monitoring data for foods, thus still overestimating the cumulative risk picture.
- Any further level of refinement beyond Tier 4 would involve extensive resources and is beyond a screening-level evaluation. If the single pesticide chemical assessment includes limited additional refinements such as use of monitoring and/or usage (e.g., percent crop treated), consideration should be given on how the refinements could be included in a screening cumulative assessment (See Figure 1).

3.2.4. Tiered Approach for Cumulative Screening-Level Residential Exposure Analysis

As noted above the single pesticide chemical risk assessments provide the primary source of residential exposure information for the cumulative screening-level residential assessment. Most residential exposure assessments that are conducted by OPP are unrefined. Specifically, they often include high-end, default assumptions with regards to surface residues (i.e., turf residues, indoor surface residues, etc.). In addition, they rarely utilize survey data in order to determine co-occurrence of exposure scenarios. Any differences in terms of level of refinement when considering these single pesticide chemical residential exposure assessments together will need to be characterized by the reviewer. Any refinements discussed in the residential tiers below would be in addition to those already in place in the single pesticide chemical assessments. These residential exposures would then be scaled using the screening-level RPFs and PODs and summed. Conceptually, the reviewer will systematically work through the tiers described below and stop refinements at the point when the residential risk does not exceed the level of concern.

- *Tier 1: Unrefined Assessment*. Residential exposures from the most recent risk assessment(s) are extracted then RPF-scaled and summed. This assessment utilizes any chemical specific surface residue data consistent with its use in each single pesticide chemical assessment but does not translate the data to the members of the candidate CMG. In summing these exposures, this assessment assumes that all residential exposure for each individual scenario (e.g., turf, pet, and indoor residential exposures) is to the single pesticide chemical in the CMG with the highest risk (i.e., lowest margin of exposure or MOE). For example, if there are three chemicals in the candidate CMG with pet uses, it is conservatively assumed that all pet use exposure occurs via the chemical with the highest risk. With respect to co-occurrence of exposure scenarios, the assumption is complete co-exposure for all of the available exposure scenarios (e.g., turf, pet, and indoor residential exposures) without any related co-exposure refinements.
- *Tier 2: Refine Surface Residue Assumptions.* Residential exposures from the most recent risk assessment(s) are extracted and it is determined if each assessment uses any pesticide chemical specific surface residue data (e.g., turf residues, indoor surface residues, etc.). If such data is utilized then the exposures are not altered. If such data is not utilized, then the chemical-specific data that results in the highest surface residue for that exposure scenario is translated and used in refined residential exposure estimates. For example, if three chemical-specific indoor residue studies are available for a candidate CMG that contains seven chemicals, the indoor residue study that results in the highest residue would be translated to the four chemicals in the class for which there are not chemical-specific indoor residue studies. These residential exposures are then RPF-scaled and summed. In summing these exposures, this assessment still assumes that all residential exposure for each individual scenario (e.g., turf, pet, and indoor residential exposures) is to the single pesticide chemical in the CMG with the highest risk (i.e., lowest MOE). With respect to co-occurrence of exposure scenarios, the assumption is complete co-exposure for all of the available

exposure scenarios (e.g., turf, pet, and indoor residential exposures) without any related co-exposure refinements.

- *Tier 3: Refine Co-occurrence Across Exposure Scenarios.* In Tier 3, the same refinements regarding the surface residue data are incorporated. These residential exposures are then RPF-scaled and summed. In summing these exposures, this assessment still assumes that all residential exposure for each scenario (e.g., turf, pet, and indoor residential exposures) is to the most potent single pesticide chemical in the CMG. With respect to co-occurrence of exposure scenarios, this assessment would determine the co-occurrence of the available exposure scenarios (e.g., turf, pet, and indoor residential exposures) using available survey data.
- Any further level of refinement beyond Tier 3 would involve extensive resources and is beyond a screening-level evaluation (See Figure 1).

3.2.5. Cumulative Screening-Level Multi-Pathway Exposure Analysis

As noted in the dietary and residential exposure sections above, the reviewer will systematically work through the dietary and residential exposure tiers and stop refinements at the point when the risks are less than the level of concern. The same stepwise approach should be taken for combining dietary and residential exposures. Initially, the reviewer would take the appropriate refined level dietary exposure point estimate and deterministically aggregate it with the appropriate refined level residential exposure point estimate. This means that the reviewer may be aggregating a more refined dietary exposure with a less refined residential exposure (i.e., Tier 3 dietary with a Tier 1 residential). In some cases, this aggregate exposure may result in risks that exceed the level of concern, which may result in the need to further refine either the dietary or residential exposure component.

There may be cases where screening-level risks are still above the level of concern at the highest Tiers described above. Refinements beyond this point would result in an exposure analysis that is no longer considered 'screening-level.' As such, the Agency will consider whether additional toxicology data are needed to further describe the MOA/AOP of the candidate CMG to help inform whether a more refined CRA as described by the 2002 guidance is warranted. If additional information or further refinement are deemed not warranted, the findings of the screening-level analysis will have the same weight as results of any CRA conducted under the 2002 guidance.

4.0. Screening-Level Cumulative Analysis & Recommendations for Next Steps

This guidance document is intended to assist Agency scientists and regulators in fulfilling the obligations of section 408(b)(2)(D)(v) to consider available information concerning cumulative effects of pesticides and other substances that have a common mechanism of toxicity. This guidance document presents a screening-level approach to evaluate whether currently available toxicology information support establishing a candidate CMG and if so, describes a screening-level approach with more refined tiers for assessing the potential cumulative risk of that candidate CMG. The screening-level cumulative approach described here uses point-

estimate aggregate methodology combined with conservative assumptions of high-end dietary (food and water) exposure with high-end residential exposure while assuming co-occurrence of dietary and residential exposure. The Agency considers this approach to be *highly conservative*. The screening-level approach presented in section 3 of this document does not specifically address incorporation of various potential CRA refinements, which help provide more accurate estimates of human risk such as PBPK modeling, probabilistic exposure modeling, and spatial or temporal considerations. These refinements are generally resource intensive, may require large amounts of toxicology and exposure data, and can involve sophisticated modelling. However, if a screening-level CRA is performed and risks do not exceed the level of concern, then there is no need to invest the resources in further refinement at that time. This CRA screening-level approach will ultimately allow the Agency to address the FFDCA requirements to consider available information concerning cumulative effects of pesticides having a common mechanism of toxicity while efficiently using resources.

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